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(54) Title: PROCESS FOR THE PREPARATION OF ANHYDROUS AZITHROMYCIN

(57) Abstract: The present invention provides a stable form of azithromycin derivatives that act as antibiotics. These compound are in anhydrous form and have increased stability over the hydrated forms.

PROCESS FOR THE PREPARATION OF ANHYDROUS AZITHROMYCIN

Azithromycin is a well known semi synthetic macrolide antibiotic (U. S. Patent
5 Nos. 4,474,768 and 4,517,359), which is prepared through the ring expansion to incorporate a nitrogen atom in the macrolide ring of erythromycin A, followed by reductive methylation. This provides an antibiotic having more stability and greater effectiveness than erythromycin-A.

10 The ring expansion and subsequent conversion of erythromycin-A to provide azithromycin is described in several U. S. Patent No. 4,474,768 (e.g. Example 3). Generally the synthesis requires several steps. The product obtained is one of the hydrated versions, either monohydrate or dihydrate.

15 Azithromycin monohydrate is hygroscopic and thus, difficult to maintain in the monohydrated form. U. S. patent 4,963,531 and EP application 298,650 (each a process for preparing azithromycin dihydrate. The process requires preparing a solution of azithromycin monohydrate in tetrahydrofuran and water. The azithromycin dihydrate is obtained by crystallization upon
20 addition of hexane.

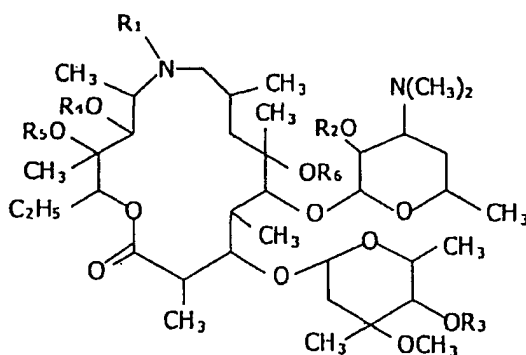
However, in U.S. Patent 4,963,531 it is reported that on storage at low humidity the azithromycin dihydrate lost water. In addition, a sample of azithromycin mono and dihydrate stored at higher humidity rapidly absorbed water. Thus,
25 the water percentage (percent hydration) in the crystals can vary depending on the relative humidity during storage. This variability of the percent hydration can make it difficult to accurately determine the proper amount of active ingredient needed when preparing dosage forms.

30 Thus, it would be useful to have a stable form of azithromycin that can be accurately measured when preparing the active ingredient forms. In addition

it would be useful to have a form of azithromycin that has increased stability and less variability in its percent hydration.

Summary of the invention

The present invention provides a stable form of azithromycin derivatives that act as antibiotics. These compounds are in anhydrous form and have increased stability over the hydrated forms. Accordingly there is provided an anhydrous compound of Formula I :



(1)

Wherein R1 represents hydrogen (C1-C8)-alkyl, (C8-C10)-aryl or (C7-C16)-aralkyl wherein the R2, R3, R4, R5 and R6 groups individually are hydrogen or (C1-C6)alkyl and a process for preparing the compound of Formula I. The process comprises removing an organic solvent from a solution comprising the hydrated compound of Formula I in the organic solvent or a solution of the hydrated compound of Formula I in a mixture of the organic solvent and water so as to provide the anhydrous compound.

The solvents that are useful in practicing the present invention are C7-C6 alcohols or halo(C1-C6) alkanes. Examples of suitable solvents for practicing the invention are alcohols such as, for example, n-propanol, 2-propanol, n-butanol,

2-butanol, n-pentanol, 2-pentanol, 3-pentanol and the like; or halo (C1-C6) alkanes such as, for example, methylene chloride, chloroform, carbon tetrachloride, 1,1,1-trichloroethylene, 1,1,2-trichloroethylene and the like.

- 5 The invention also provides a pharmaceutical composition comprising an anhydrous compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

10 Additionally, the invention provides a method for treating a microbial infection in a mammal such as a human, which comprises administering to a mammal an antimicrobially effective amount of azithromycin in a suitable dosage form.

Brief description of the figures

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FIG-1 illustrate the Infrared spectrum of the anhydrous azithromycin of the invention.

FIG-2 illustrate the Infrared spectrum of the azithromycin dihydrate.

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FIG-3 illustrate the DSC spectrum of the anhydrous azithromycin of the invention.

FIG-4 illustrates the DSC spectrum of the azithromycin dihydrate.

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FIG-5 illustrates the XRD spectrum of the anhydrous azithromycin of the invention.

FIG-6 illustrates the XRD spectrum of the azithromycin dihydrate

Detailed description

The following definitions are used, unless otherwise described halo is fluoro, chloro, bromo, or iodo. Alkyl denotes both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic optically active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by crystallization techniques, by synthesis from optically active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine nicotine against activity using the standard tests described herein, or using other similar tests which are well known in the art.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C1-C6) alkyl can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, n-pentyl, 3-pentyl, or hexyl; halo (C1-C6) alkyl can be isomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; C3-C6 alcohols can be 1-hydroxypropane, 2-hydroxypropane, 3-hydroxypropane, 1-

hydroxybutane, 2-hydroxybutane, 1-hydroxypentane, 2-hydroxypentane, 1-hydroxyhexyl, or 6-hydroxyhexane and the like; aryl can be phenyl, indenyl or naphthyl.

5 A specific value for R1 is CH3.

A specific value for each of R2, R3, R4, R5 and R6 is hydrogen.

A preferred group of compounds are compounds of Formula I; or a
10 pharmaceutically acceptable salt thereof.

Another preferred group of compounds are compounds of Formula I wherein R1 is a lower alkyl group having from 1 to 4 carbon atoms and each of R2, R3, R4, R5 and R6 is hydrogen.

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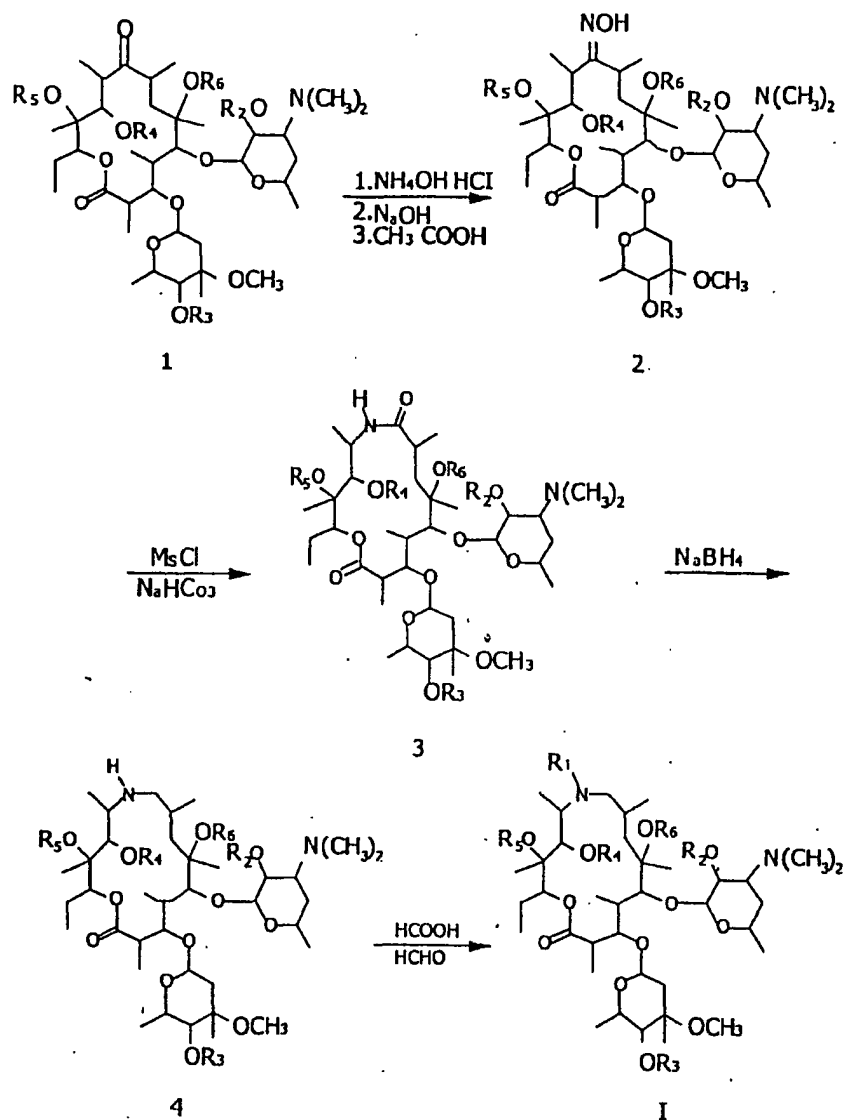
A preferred compound of the invention is a compound of where R1 is methyl and each of R2, R3, R4, R5 and R6 is hydrogen or a pharmaceutically acceptable salt thereof.

20 The preferred alcohol solvents for practicing the present invention are n-propanol, 2-propanol, n-butanol or 2-butanol. Most preferred is 2-propanol. The preferred haloalkane solvents for practicing the present invention are methylene chloride, chloroform and carbon tetrachloride. Most preferred is chloroform.

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The preparation of the compounds of the invention can be performed according to the procedures disclosed in US Patent Nos. 4,328,334, 4,474,768 and 4,517,357. The specific process for is illustrated in Scheme 1. Erythromycin A, or a derivative thereof, 1, is converted to the corresponding
30 oxime, 2. Using an excess, e.g. about 10 equivalents of hydroxyl amine. The erythromycin A oxime is rearranged via the Beckmann rearrangement with methane sulfonyl chloride at low temperature to furnish amide, 3. The amide, 3 is then reduced, with hydrogen and a catalyst or with a metal hydride, such

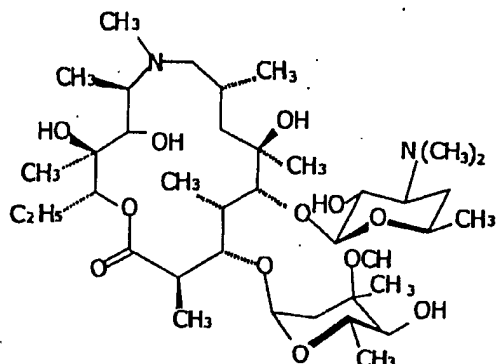
as sodium borohydride to furnish amine, 4-the amine is then alkylated, e.g. using formaldehyde in the presence of formic acid. The product, 1 is crystallized from alcohol/water to provide the hydrated azithromycin derivative.



A preferred compound of the present invention, Azithromycin is represented below

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The compound of Formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e. orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

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Thus, the present compound may be systemically administered e.g. orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may be conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such

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therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following
5 binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such
as dicalcium phosphate; a disintegrating agent such as corn starch, potato
starch, nignic acid and the like, a lubricant such as magnesium stearate; and a
sweetening agent such as sucrose, fructose, lactose or aspartame or a
10 flavoring agent such as pappermint, oil of wintergreen, or cherry flavoring
may be added. When the unit dosage form is a capsule, it may contain, in
addition to material of the above type, a liquid carrier, such as vegetable oil or
a polyethylene glycol. Various other materials may be present as coatings or
to otherwise modify the physical form of the solid unit dosage form. For
instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or
15 sugar and the like. A syrup or elixir may contain the active compound, sucrose
or fructose as a sweetening agent, methyl and propylparabenes as
preservatives, a dye and flavoring such as cherry or orange flavor. Of course,
any material used in preparing any unit dosages form should be
pharmaceutically acceptable and substantially non-toxic in the amounts
20 employed. In addition, the active compound may be incorporated into
sustained release preparation and devices.

The active compound may also be administered intravenously or
intraperitoneally by infusion or injection. Solutions of the active compound
25 or its salts can be prepared in water, optically mixed with a nontoxic
surfactant. Dispersions can also be prepared in glycol, liquid polyethylene
glycerol, triacetin and mixtures thereof and in oils under ordinary conditions
of storage and use, these preparations contain a preservatives to prevent the
growth of microorganisms.

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The pharmaceutical dosage forms suitable for injection or infusion can include
sterile aqueous solutions or dispersions or sterile powders comprising the
active ingredient which are adapted for the extemporaneous preparation of

sterile injectable or infusible solution or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, 5 water, ethanol a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols and the like), vegetable oils, non-toxic glyceryl esters and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of 10 the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in 15 the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of 20 the other ingredients enumerated above as required followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solution, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient (plus any additional desired ingredient present in the previously 25 sterile filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e. when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination 30 with dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers

include water, alcohols or glycols or water-alcohol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use.

- 5 The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed on to the affected area using pump type or aerosol sprayers.

- 10 The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

- 15 In general, however, a suitable dose will be in the range of from about 1 mg/Kg to 200 mg/Kg of body weight per day. Favoured dosage range is from about 5 mg/Kg to about 100 mg/Kg of body weight per day and preferred range is about 5 mg/Kg to about 50 mg/Kg of body weight per day.

- 20 The compound is conveniently administered in unit dosage form; for example containing 25 mg to 3000 mg, conveniently 200 mg to 2000 mg, most conveniently 250 mg to 600 mg of active ingredient per unit dosage form.

The invention will now be illustrated by the following non-limiting.

Examples :**Example 1 : Erythromycin-A Oxime**

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A solution of 1.40 Kg of hydroxylamine hydrochloride in isopropyl alcohol and water was prepared. Sodium hydroxide, 0.81 Kg, was added in portions, at temperature of about 20°C. After the addition the pH was adjusted to 7.0 with acetic acid. Erythromycin base, 1.5 Kg was added to this solution, and it was maintained at 45-55°C for 28 hours.

The reaction mixture was cooled to room temperature and the reaction terminated by the addition of ammonia water mixture. The crude product was treated with water to remove inorganic salts and to furnish the title product as white crystalline material, 1.40 Kg.

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Example 2 : 9a-aza-9a-homoerythromycin

The title product prepared in Example 1, 1.25 Kg was dissolved in acetone and water and maintained at lower temperature. The pH of the reaction mixture was adjusted to about 2.5 to about 2.8 with hydrochloric acid. Sodium bicarbonate 0.48 Kg was added in portions to in cooled reaction mixture. After addition of sodium bicarbonate 0.5 Kg methane sulfonyl chloride 0.5 Kg were added. After stirring for 1 hour at low temperature the pH of the reaction mixture was adjusted with sodium hydroxide and the title product was filtered off as a white crystalline material in high purity. Yield 1.00 Kg.

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Example 3 : 9-Deoxo-9a-aza-9a-homoerythromycin

The title product prepared in Example 2, 1.00 Kg was stirred in methanol and water. Sodium borohydride 1 Kg was added over four hours. The temperature was maintained below 5°C. After the completion of the sodium borohydride addition, the reaction mixture was stirred for an additional six

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hours at $>5^{\circ}\text{C}$ and for an additional twenty four hours, at room temperature. The reaction was terminated by the addition of water and chloroform. The chloroform layer was separated and washed with fresh water. The product was extracted by pH adjustment using dilute hydrochloric acid and sodium hydroxide the mixture was stirred at pH 2.5 to 2.8 for 2 hours. The pH was adjusted to 9.5 to 9.8 and stirred for 1 hour. The water layer was separated and an additional portion of water was added and the extraction repeated two additional times. After third extraction the chloroform extracts were separated, dried over potassium carbonate, filtered and used in the next step without additional treatment.

Example 4 : 9-deoxa-9a-methyl-9a-aza-9a-homoerythromycin-A

The title product prepared in Example 3, was treated with formaldehyde, 0.17 L, and formic acid 0.105, the reaction mixture was stirred for four hours under nitrogen and heated at reflux for twelve hours. The reaction was cooled, treated with water and the pH was adjusted to 4.0 to 4.5. Chloroform was added and the mixture stirred and the chloroform layer separated. The aqueous layer was extracted twice with chloroform. Water was added to the extracts and the pH was adjusted under stirring to constant to pH 2.0 to 3.0 with dilute hydrochloric acid. The mixture was stirred vigorously and the chloroform layer was separated. This was repeated five times.

The aqueous layers were made basic to pH 6.0 to 6.5 with dilute sodium hydroxide and extracted twice with chloroform. The chloroform layers were combined, dried over K_2CO_3 and concentrated under vacuum. The solid residue was dissolved in isopropyl alcohol and the title product crystallized by adding water. The yield of azithromycin was 0.55 Kg.

Example 5 : Azithromycin Dihydrate

The title product, 0.5 Kg, prepared in Example 4, was dissolved in water, making the solution acidic (pH 2.5 to 5.0) with dilute hydrochloric acid. After

20 minutes stirring the pH was raised with dilute sodium hydroxide and the solution was stirred for twelve hours. The product was crystallized as a white crystalline material in high purity. Yield 0.48 Kg.

5 **Example 6 : Anhydrous Azithromycin**

The azithromycin dihydrate prepared in Example 5, or the azithromycin monohydrate prepared in Example 4, 500 gm was dissolved in isopropanol, 3 L. The solution was heated and the alcohol was distilled to remove the water.

- 10 After the solvent was removed the residue was dried under vacuum to provide the anhydrous azithromycin. Yield 0.47 Kg. Purity \geq 96%.

Example 7 : Anhydrous Azithromycin

- 15 The azithromycin dihydrate prepared in Example 5, or the azithromycin monohydrate prepared in Example 4, ~ 100 gm was dissolved in chloroform and water 1.7 L (0.7 : 1). The solution was heated and the solvent was distilled off. After the solvent was removed the residue was dried under vacuum to provide the anhydrous azithromycin. Yield 94 g, purity \geq 96%.

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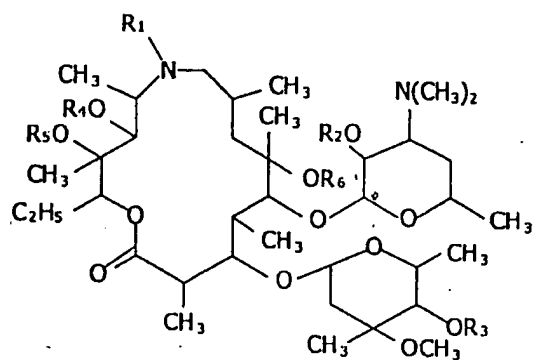
- All publications, patents and patent documents cited in the specification are incorporated by reference herein, as though individually incorporated by reference. In the case of any inconsistencies, the present disclosure including any definitions therein will prevail. The invention has been described with
25 reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims :

1. A process for presenting an anhydrous compound having formula I :

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I

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Wherein, R1 represents (C1-C6)-alkyl (C6-C10)-aryl or (C7-C16)-aralkyl; wherein R represents an, and each R2, R3, R4, R5 and R6 individually represents hydrogen or (C1-C4) alkyl; comprising removing an organic solvent from a solution comprising a hydrogen compound Formula I in the organic solvent or a solution of a hydrated compound of Formula I in a mixture of the organic solvent and water so as to provide the anhydrous compound.

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2. A process according to claim 1 wherein the solution comprises the hydrated compound of Formula I in the organic solvent.

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3. A process according to claim 1, wherein, the solution comprises the hydrated compound of Formula I in a mixture of the organic solvent and water.

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4. A process according to claim 2 or 3, wherein the solvent is a C4-C6 alcohol or a halo (C1-C6) alkane.

5. A process according to claim 4, wherein the solvent is selected from the group consisting of n-propanol, 2-propanol, n-butanol, n-pentanol, 2-pentanol and 3-pentanol.
- 5 6. A process according to claim 5, wherein the solvent is n-propanol, 2-propanol, n-butanol or 2-butanol.
7. A process according to claim 6, wherein, the solvent is 2-propanol.
- 10 8. A process according to claim 4, wherein the solvent is a halo(C1-C6) alkane.
9. A process according to claim 8, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, carbon tetrachloride 1,1,1-trichloroethylene and 1,1,2-trichloroethylene.
- 15 10. A process according to claim 9, wherein the solvent is selected from the group consisting of methylene chloride, chloroform, and carbon tetrachloride.
- 20 11. A process according to claim 11, wherein the solvent is chloroform.
12. A process according to claim 1, wherein R1, R2, R3, R4, R5 and R6 is hydrogen.
- 25 13. A process according to claim 1, wherein R1 is (C1-C6)-alkyl, (C6-C10)-aryl or (C7-C16)-aralkyl and each R2, R3, R4, R5 and R6 is hydrogen.
14. A process according to claim 13, wherein R1 is (C1-C6)-alkyl.
- 30 15. A process according to claim 14, wherein R1 is methyl or ethyl.

16. A process according to claim 15, wherein R1 is methyl.
17. A process to claim 1, wherein the compound of Formula I is azithromycin.

FIG. 1 INFRARED SPECTRUM OF THE ANHYDROUS AZITHROMYCIN

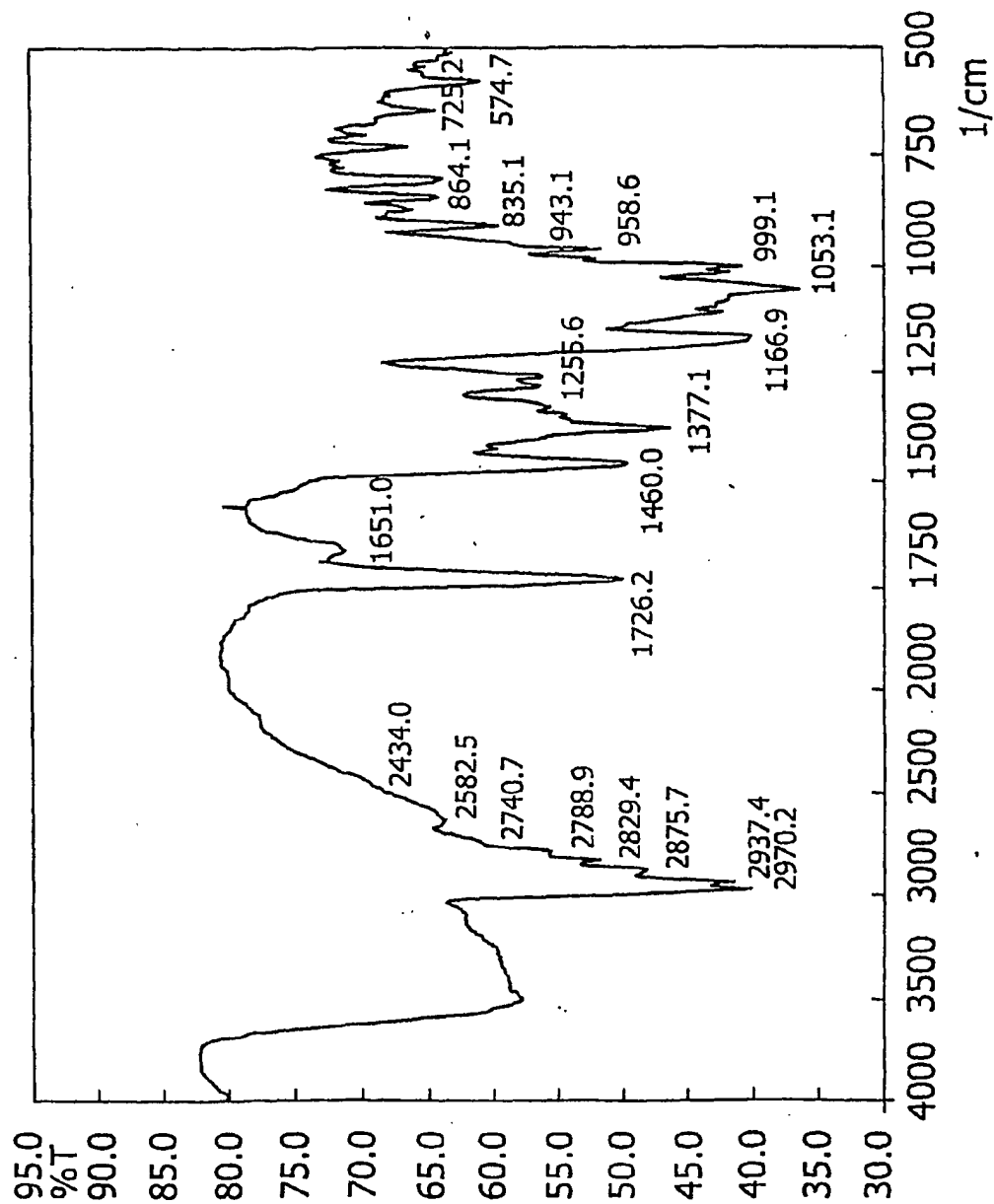


FIG. 2 INFRARED SPECTRUM OF THE AZITHROMYCIN DIHYDRATE

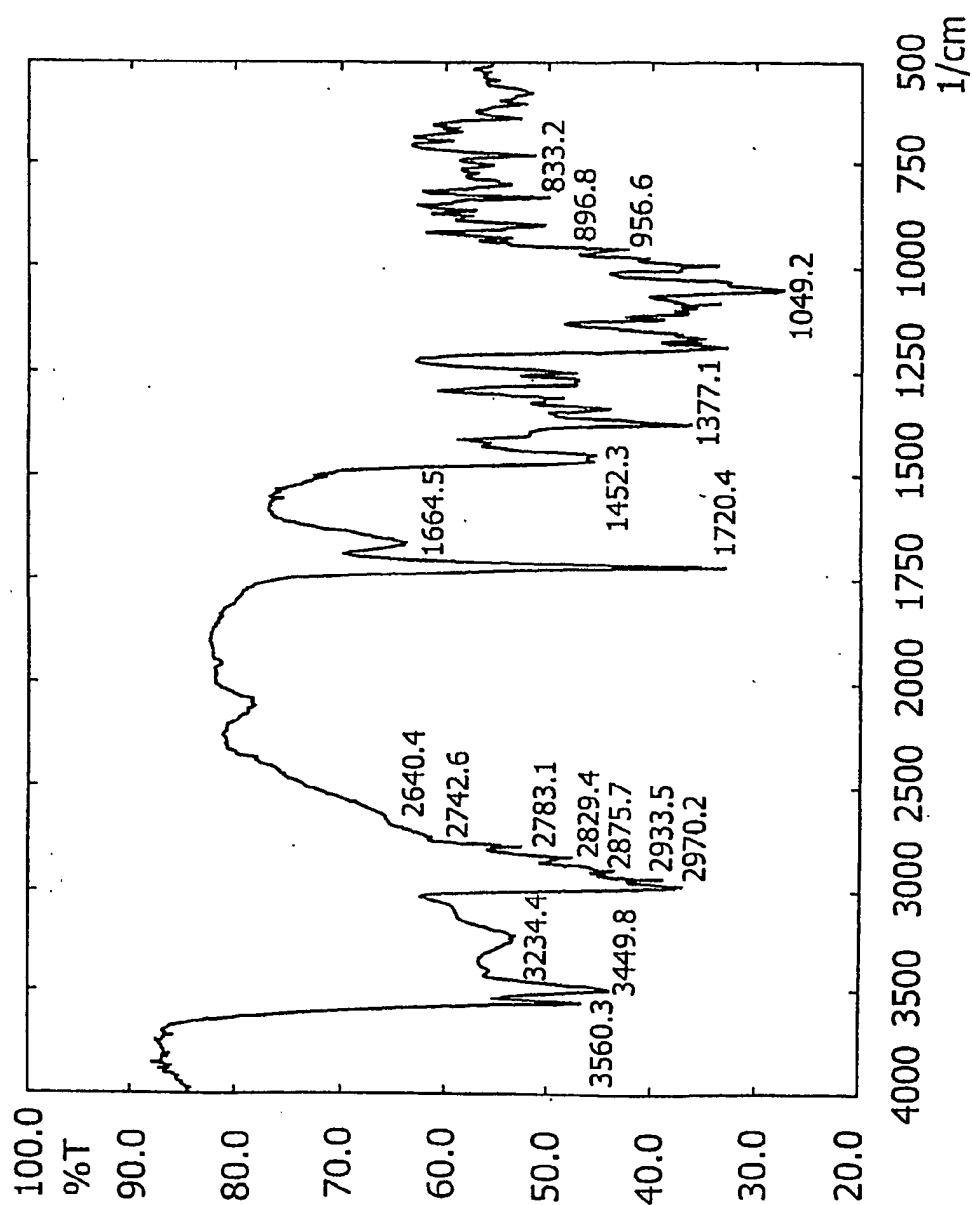


FIG. 3 DSC SPECTRUM OF THE ANHYDROUS AZITHROMYCIN

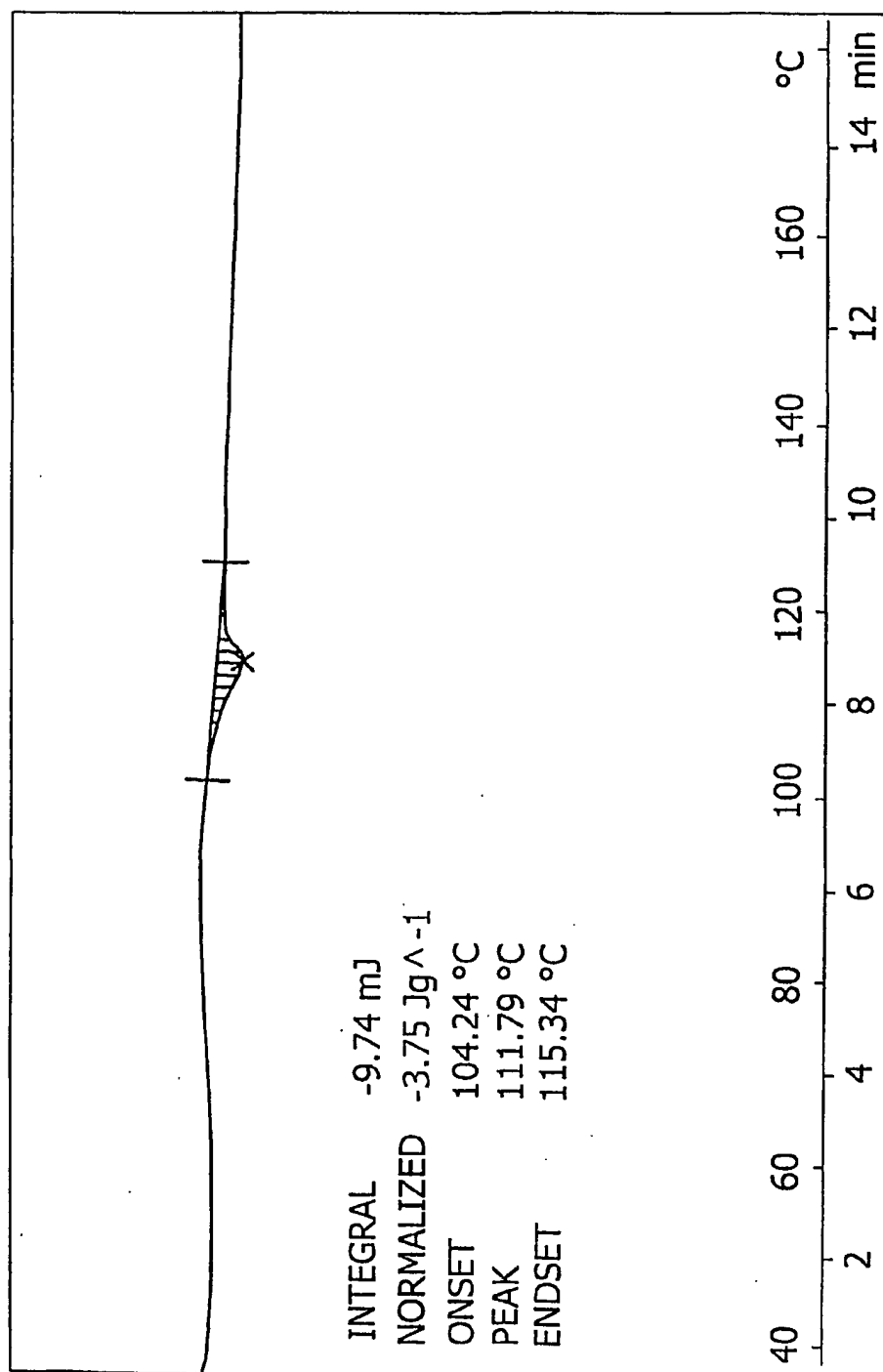
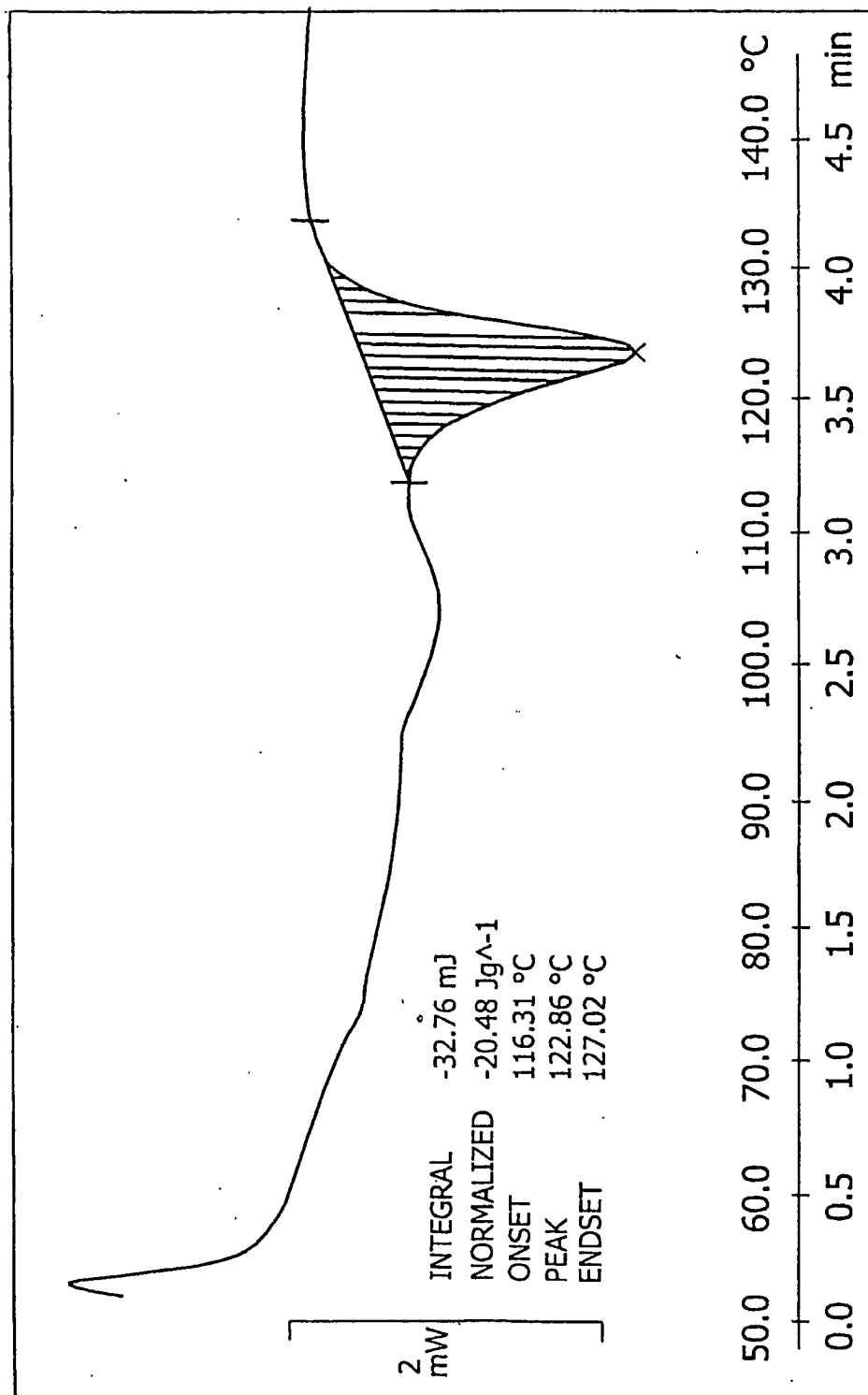


FIG. 4 DSC SPECTRUM OF THE AZITHROMYCIN DIHYDRATE



XRD SPECTRUM OF THE ANHYDROUS AZITHROMYCIN

FIG. 5

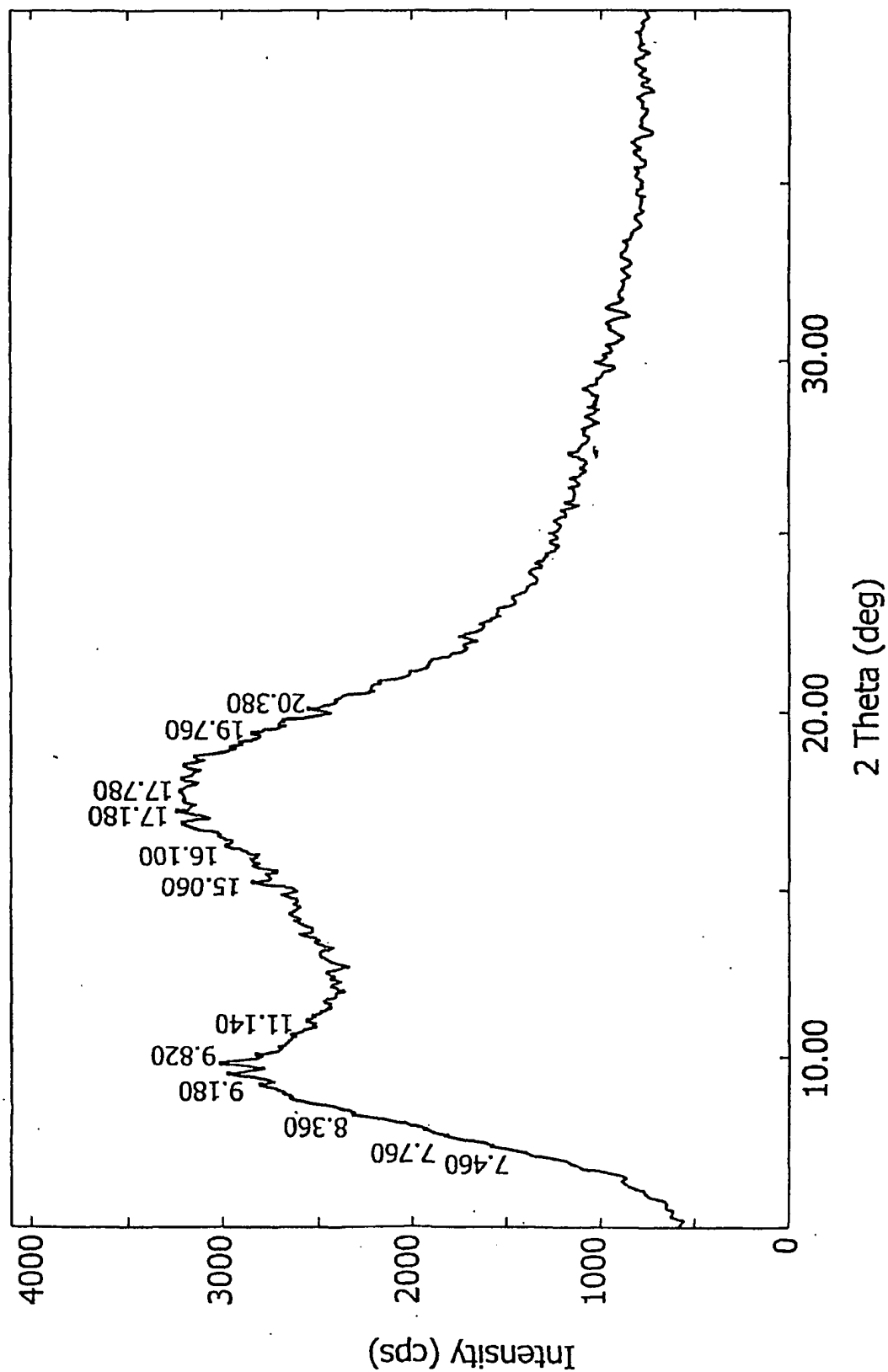
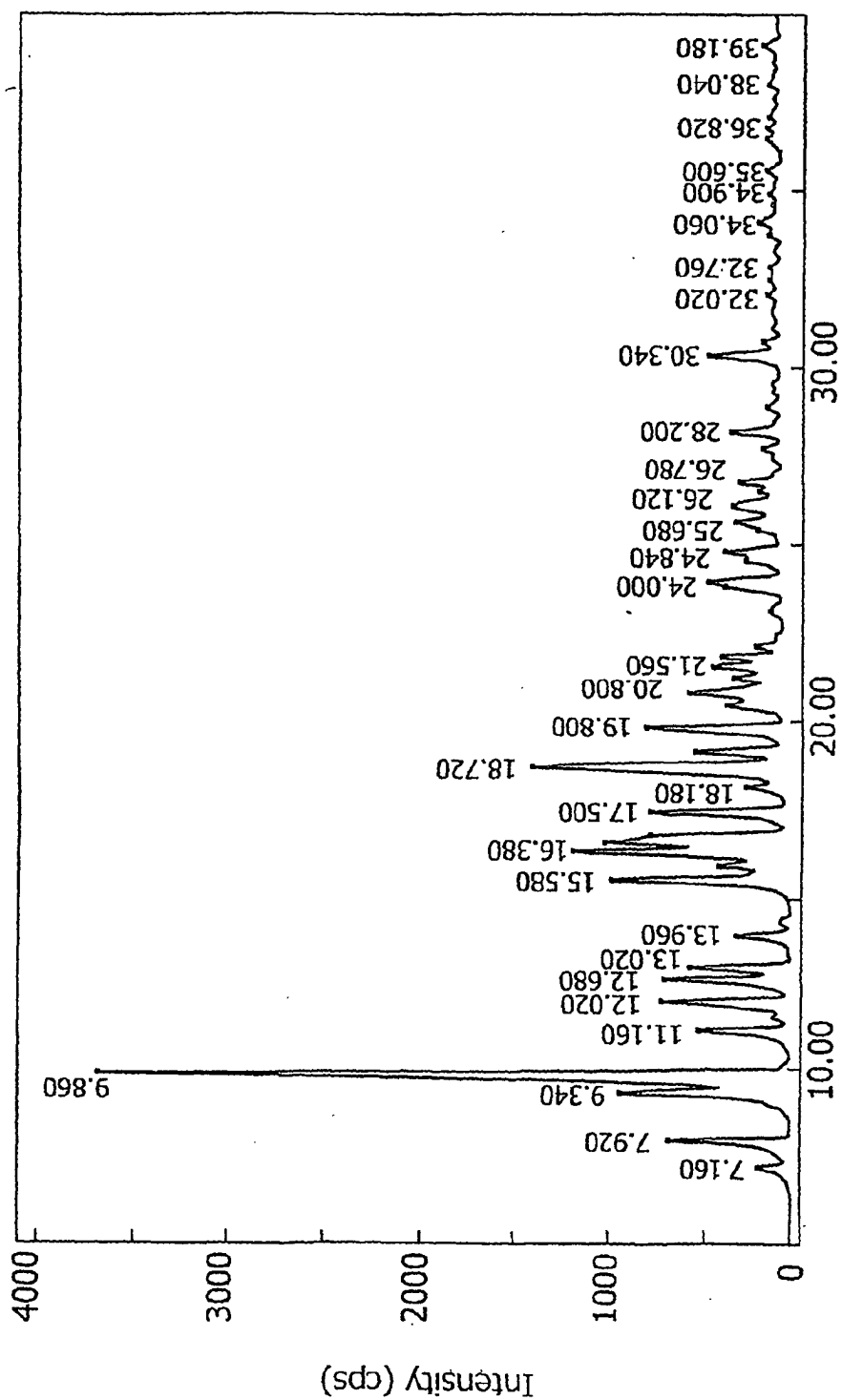


FIG. 6 XRD SPECTRUM OF THE AZITHROMYCIN DIHYDRATE



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER																				
IPC(7) : C08J 9/28																				
US CL : 536/127																				
According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED																				
Minimum documentation searched (classification system followed by classification symbols) U.S. : 536/127																				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
X,E	US 6,245,903 B1 (Karimian et al) 12 June 2001 (12.06.2001), column 1, lines 47-57.	1, 2, 8-11, 13-17																		
X	WO 99/58541 (BOSCH) 18 November 1999 (18.11.1999), pages 7-8; page 10, lines 5-10.	1, 2, 4-7, 13-17																		
A	US 5,441,939 (YANG) 15 August 1995 (15.08.1995).	1-17																		
A	US 5,350,839 (ASAKA et al) 27 September 1994 (27.09.1994).	1-17																		
A	US 4,963,531 (REMINGTON) 16 October 1990 (16.10.1990).	1-17																		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"> <tr> <td colspan="2">Special categories of cited documents</td> <td></td> </tr> <tr> <td>"A"</td> <td>document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E"</td> <td>earlier application or patent published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"I"</td> <td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date or another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O"</td> <td>document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P"</td> <td>document published prior to the international filing date but later than the priority date claimed</td> <td>"&" document member of the same patent family</td> </tr> </table>			Special categories of cited documents			"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"I"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date or another citation or other special reason (as specified)	"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O"	document referring to an oral disclosure, use, exhibition or other means		"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family
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Date of the actual completion of the international search 11 February 2002 (11.02.2002)		Date of mailing of the international search report 14 MAR 2002																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PC1 Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer James Wilson Telephone No. (703)308-4358																		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN00/00073

Continuation of B. FIELDS SEARCHED Item 3:

WEST. REGISTRY. CAPLUS. USPATENT.

search terms: structure search. anhydrous. azithromycin. erythromycin